

Development and Calibration of a Hybrid Multiscale Model of Vascular Tumor Growth

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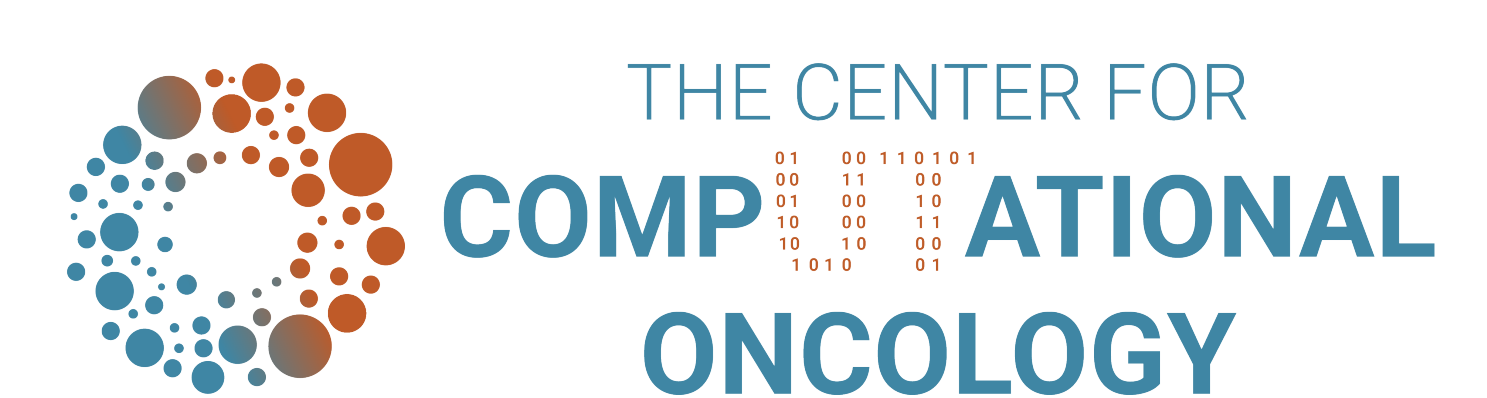
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Background

Cancer is affected by a series of events that occur at different time and length scales. Understanding these complex multiscale interactions is a crucial step towards predicting cancer growth and in developing effective therapies.

Avascular Tumor Growth Model

We integrate different modeling approaches in a hybrid multiscale model of avascular tumor growth [1]:

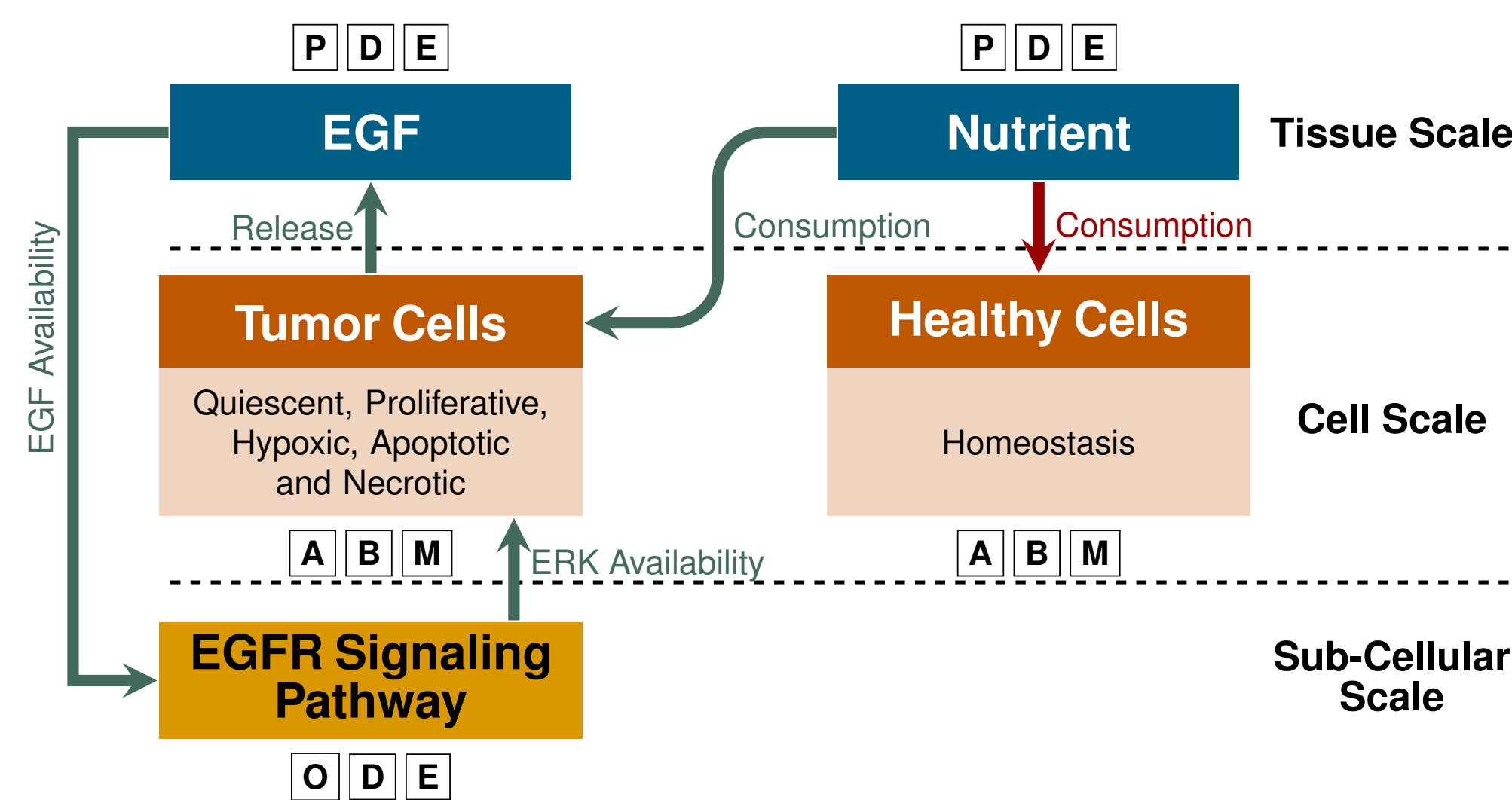


Figure 1: The nutrient and EGF dispersions that occur at the tissue scale are modeled by partial differential equations (PDEs). At the cell scale, healthy and cancer cells are described using an agent based model (ABM). The intracellular phenomena that regulate cell proliferation are described by a signaling pathway model through a system of ordinary differential equations (ODEs).

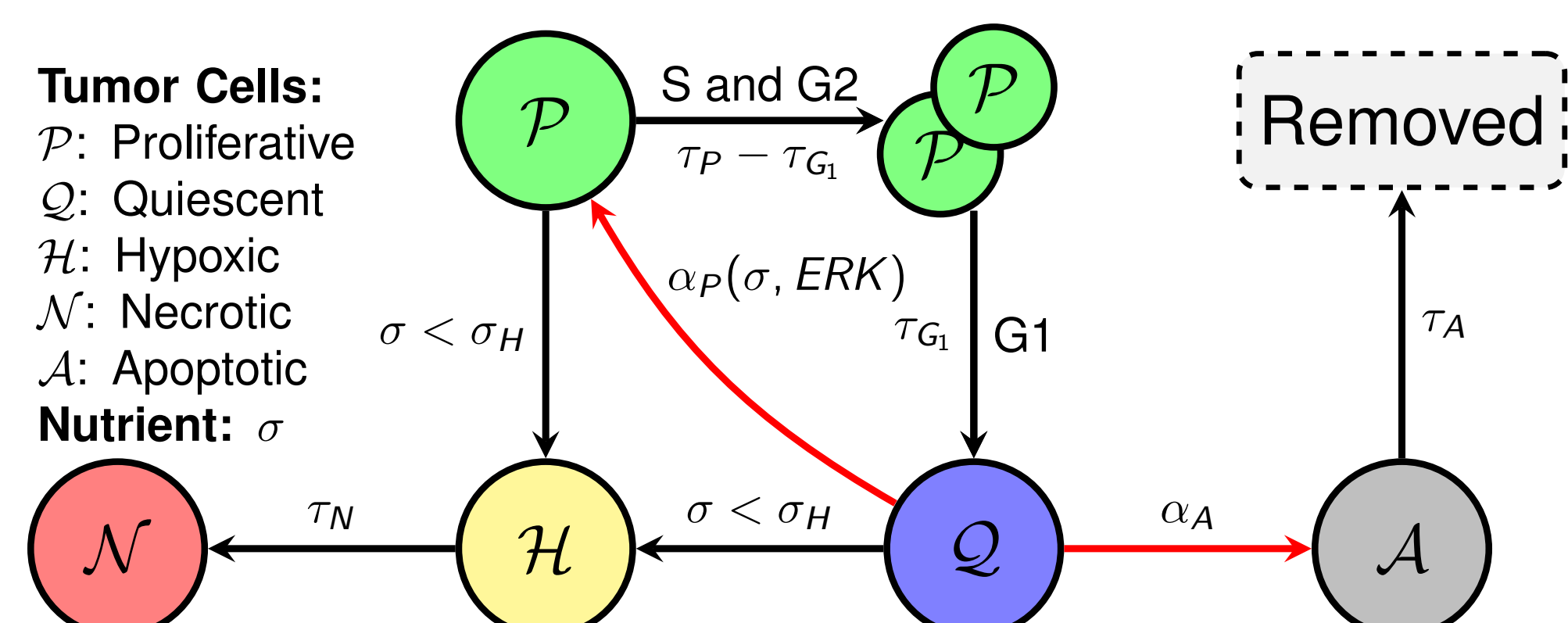
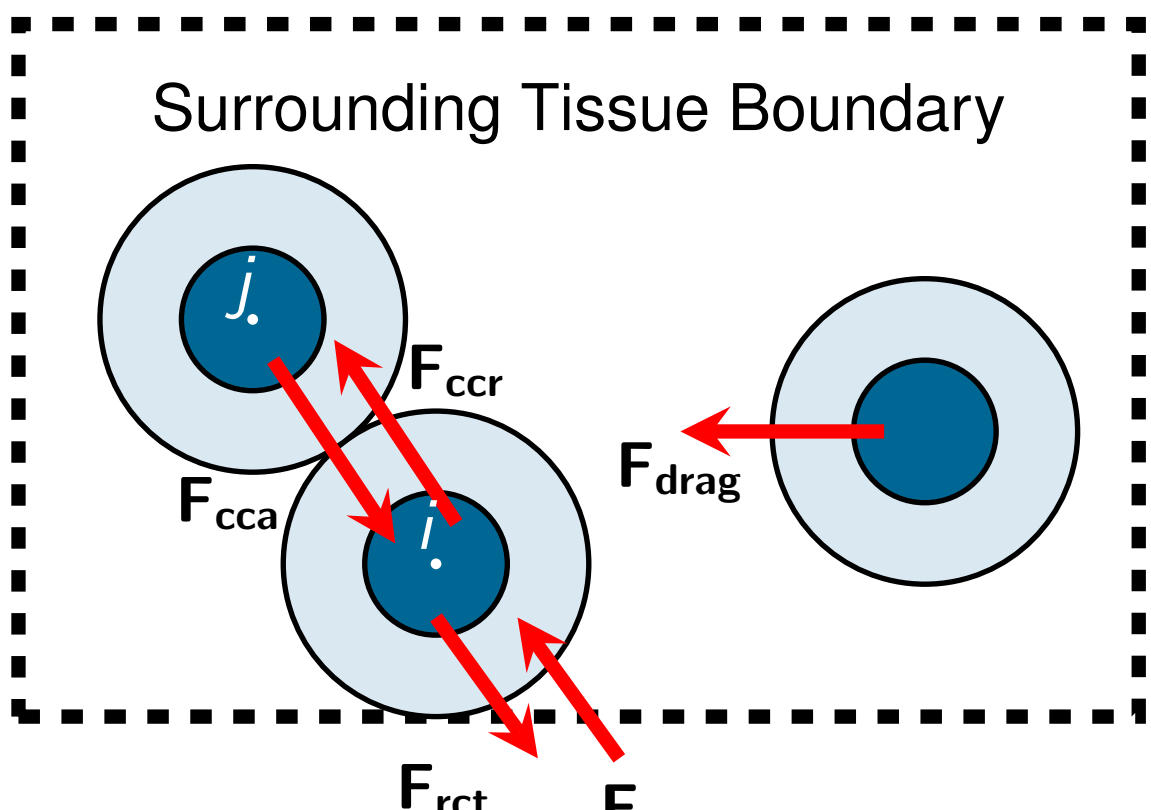


Figure 2: Schematic illustration of cancer cell transitions, that can be deterministic (black arrows) or stochastic (red arrows). Where α_P and α_A are intensity functions, τ_A , τ_P , and τ_{G1} are the apoptosis, cell cycle and G1 characteristic times, and σ_H is the hypoxic threshold.

In this model each agent is a cell that has the following properties: cell nuclear and action radius, cell state, calcification degree, position and velocity. Denoting by $N(t)$ the total number of cells, considering $F_d = -\eta v$, and Newton's second law applied to the i^{th} cell yields:

$$0 \approx m_i \dot{v}_i = \sum_{j=1}^{N(t)} (F_{cca}^{ij} + F_{ccr}^{ij}) + F_{ct}^i + F_{rct}^i + F_d^i$$



(a) Simulation at 4.17 days.

(b) Simulation at 8.34 days.

(c) Simulation at 16.68 days.

Figure 3: ABM (left), nutrient dispersion (middle), and EGF dispersion (right).

Simplified Avascular Tumor Growth Model

- Calibration data acquired using IncuCyte Live Cell Analysis.
- 3 initial confluences (low, medium and high);
- 4 glucose levels (1, 2, 5 and 10 mM);
- 4 replicas of each;
- 48 wells - area of the well 0.32cm².

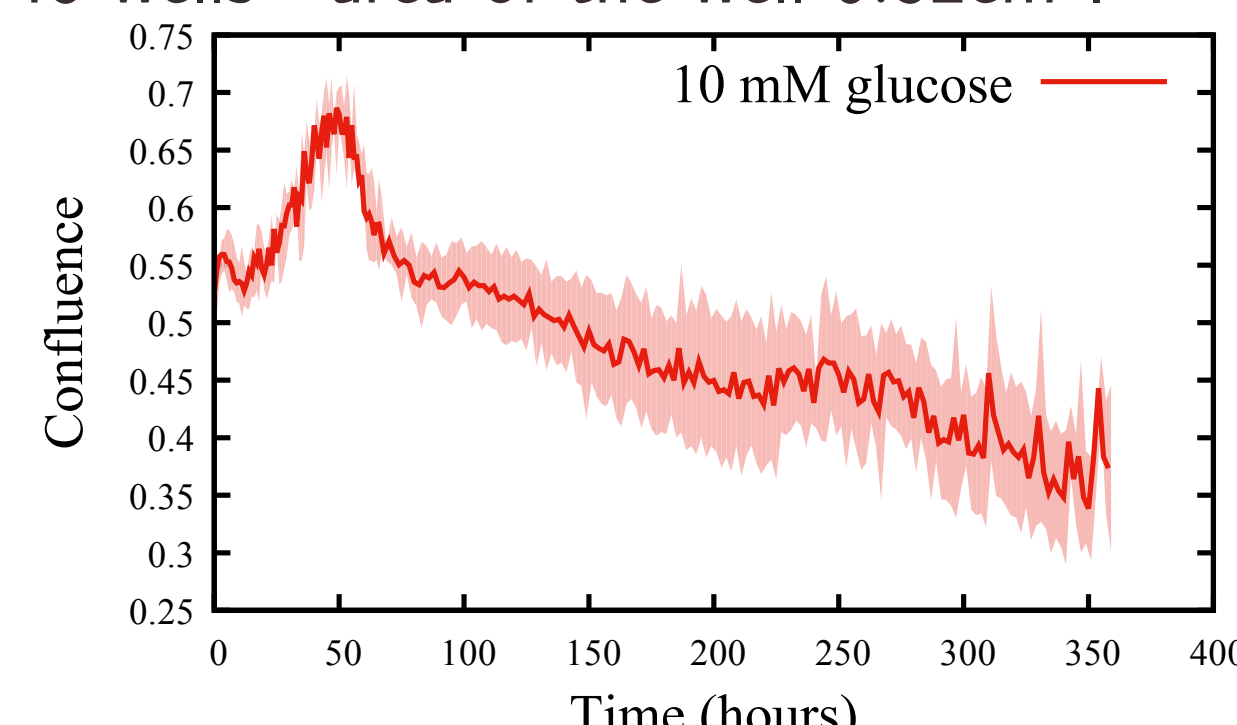


Figure 4: Mean of 4 replicas (solid line) and standard deviation.

To capture the experimental scenario, the model needs to be simplified as below:

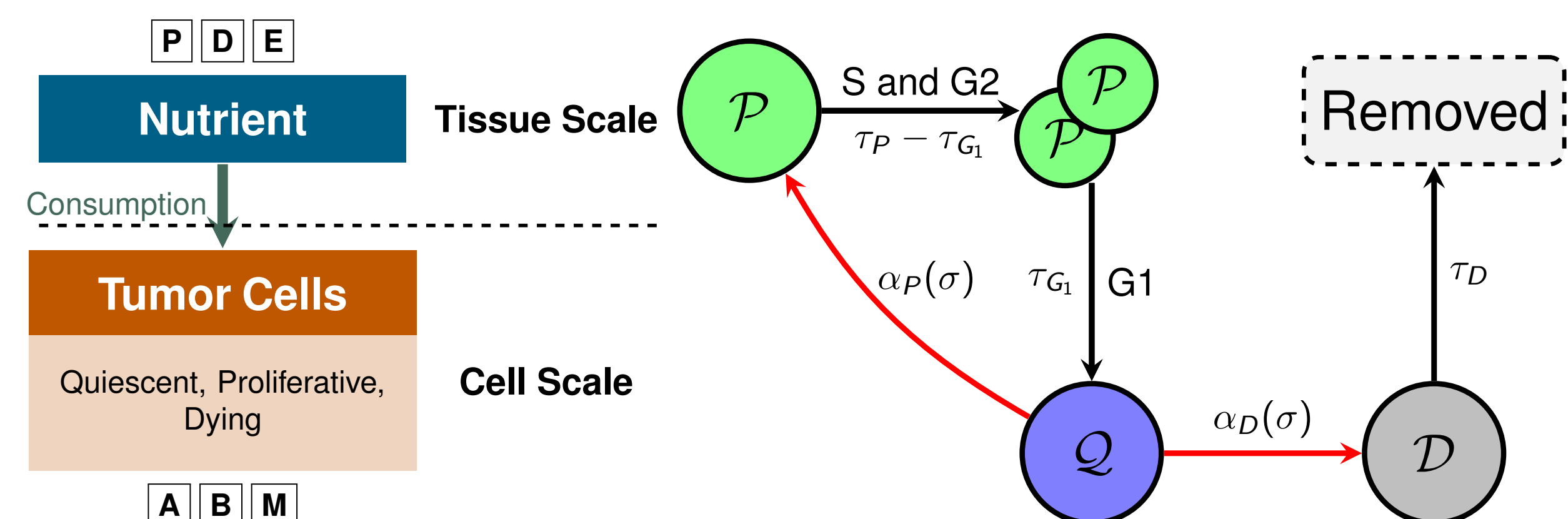


Figure 6: The hypoxic, apoptotic and necrotic are grouped and called dying cells. The healthy cells and the sub-cellular scale are removed. The death of the cells is in function of the nutrient concentration.

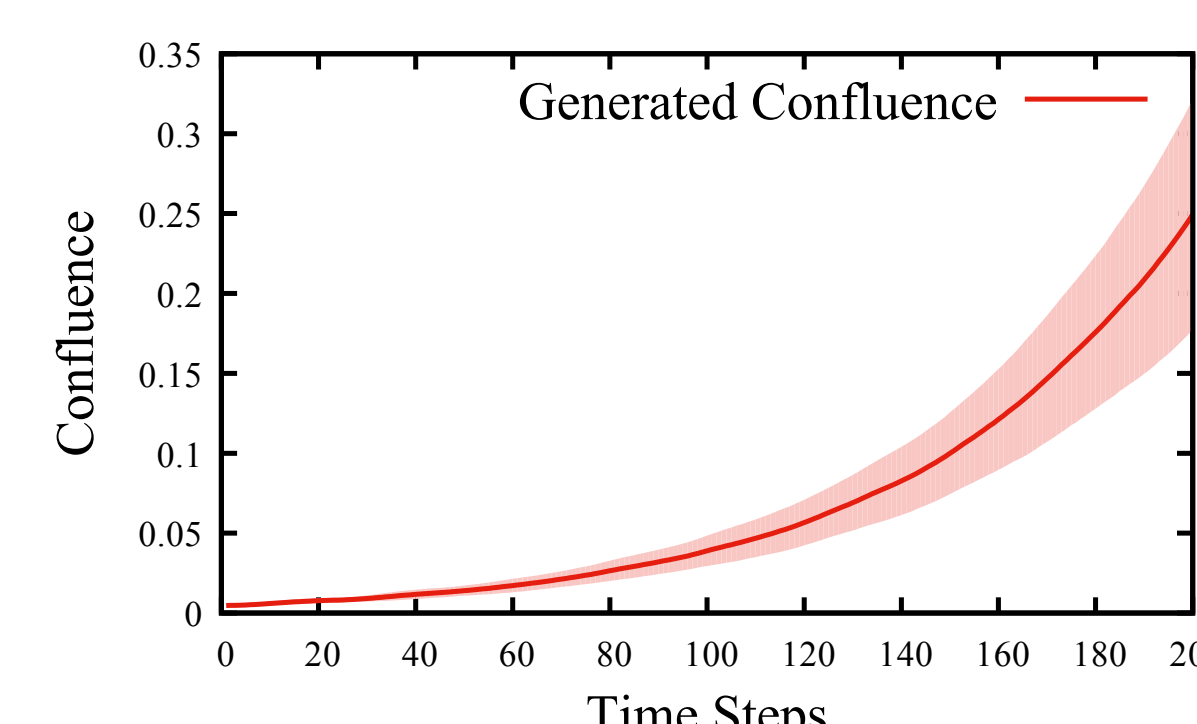


Figure 7: Mean of 10 simulations (solid line) and standard deviation.

- $\eta_{data} \sim \mathcal{N}(\mathbf{0}_{N \times 1}, \sigma_{data}^2 \mathbf{I}_{N \times N}) \rightarrow$ accounting for the data uncertainty;
- $\eta_{model} \sim \mathcal{N}(\mathbf{0}_{N \times 1}, \sigma_{model}^2 \mathbf{I}_{N \times N}) \rightarrow$ accounting for the model inadequacy.

Considering the parameter σ such as $\sigma^2 = \sigma_{data}^2 + \sigma_{model}^2$, the likelihood function

$$\pi(\hat{y}|\theta) = \prod_{i=1}^{N_i} \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{-\frac{(\hat{y}_i - \hat{d}_i(\theta))^2}{2\sigma_i^2}}$$

$\hat{d}_i(\theta)$ is the mean of M_m realizations of the stochastic model; \hat{y}_i is the mean of 4 data points.

Synthetic data: Data generated using 10 realizations of the ABM using $\alpha_P = 0.240$ and $\alpha_D = 0.110 \times 10^{-2}$.



The model is implemented in C++, the continuum model is solved using Libmesh, a finite element library. The simulations are performed with 16 - 48 processors on the Lonestar 5, TACC, UT at Austin. The model is calibrated using Markov chain Monte Carlo, the results are presented below:

Samples ($\times 10^3$)	Realizations	Calibration		Time
		α_P	$\alpha_D (\times 10^{-2})$	
16	20	0.299 (24%)	0.105 (05%)	0 d 06 h 00 min 35 s
32	20	0.314 (31%)	0.111 (01%)	0 d 12 h 59 min 02 s
48	20	0.316 (32%)	0.112 (02%)	0 d 21 h 03 min 53 s
16	40	0.277 (15%)	0.098 (11%)	0 d 12 h 00 min 10 s
16	80	0.250 (04%)	0.110 (00%)	2 d 18 h 40 min 45 s

References

- [1] H. L. Rocha, R. C. Almeida, E. A. B. F. Lima, A. C. M. Resende, J. T. Oden, and T. E. Yankeelov. A hybrid three-scale model of tumor growth. *Mathematical Models and Methods in Applied Sciences*, 28(01):61–93, 2018.

Vascular Tumor Growth Model

A mathematical model that includes the salient features of angiogenesis is required to accurately predict tumor growth past the initial stage of development.

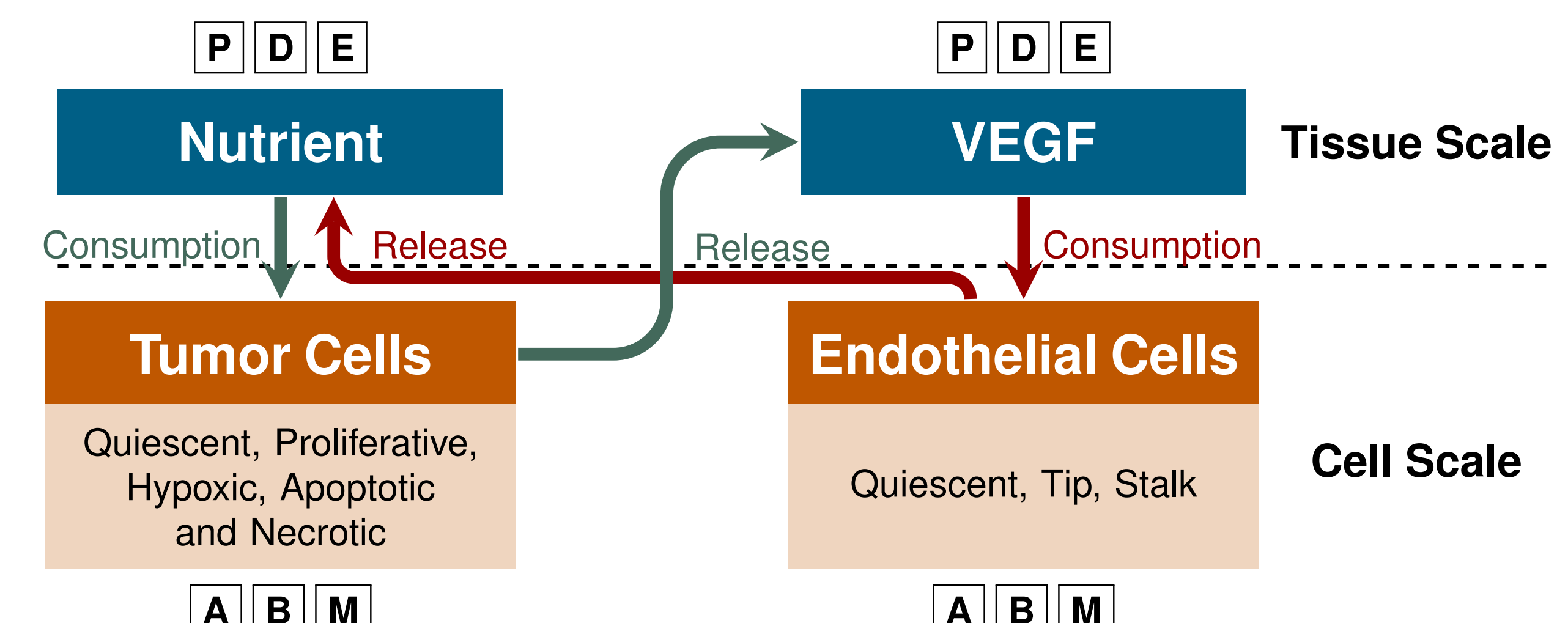


Figure 8: The nutrient and VEGF dispersions that occur at the tissue scale are modeled by partial differential equations (PDEs). At the cell scale, endothelial and cancer cells are described using an agent based model (ABM).

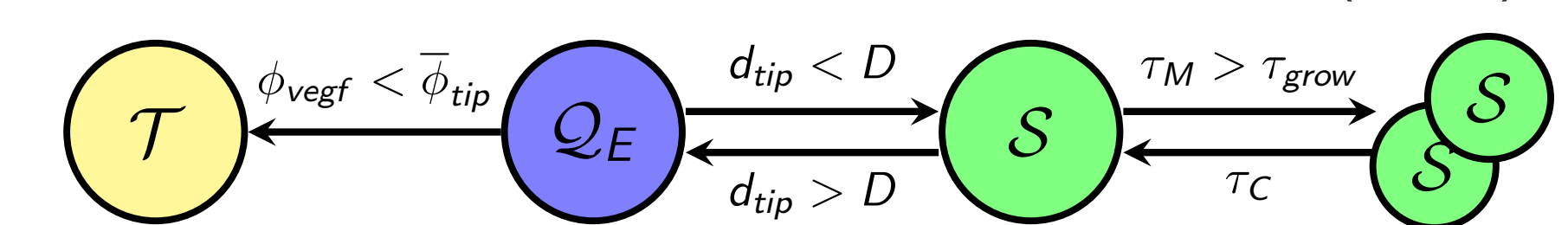


Figure 9: Endothelial cell transitions: quiescent endothelial cells (Q_E) become tip cells (T) when the VEGF concentration (ϕ_{VEGF}) is higher than the threshold ($\bar{\phi}_{tip}$). Here d_{tip} is the distance from the tip cell and τ_C is the maturation time. The stalks cells (S) divide after a characteristic time τ_M .

In this new model, the hypoxic cells can become quiescent cells when the nutrient concentration increases due to the new source of nutrient.

The nutrient (σ) and VEGF (ϕ_{veg}) concentrations at a point $x \in \Omega$ at a time $t \in (0, T_{tissue}]$ are governed by the following reaction-diffusion equations:

$$\frac{\partial \sigma}{\partial t} = \nabla \cdot (D_n \nabla \sigma) - \Lambda_n(x, t) \sigma + \Gamma_n(x, t) \sigma (1 - \sigma),$$

$$\frac{\partial \phi_{veg}}{\partial t} = \nabla \cdot (D_v \nabla \phi_{veg}) - \Lambda_v(x, t) \phi_{veg} + \Gamma_v(x, t) \phi_{veg} (1 - \phi_{veg}),$$

where D_n and D_v are, respectively, the nutrient and VEGF diffusion coefficient, $\Lambda_n(x, t)$ is the nutrient uptake rate of the cancer cells, $\Lambda_v(x, t)$ is the VEGF uptake rate of the endothelial cells, $\Gamma_n(x, t)$ is the nutrient release rate of the endothelial cell, and $\Gamma_v(x, t)$ is the VEGF release rate of the hypoxic cell.

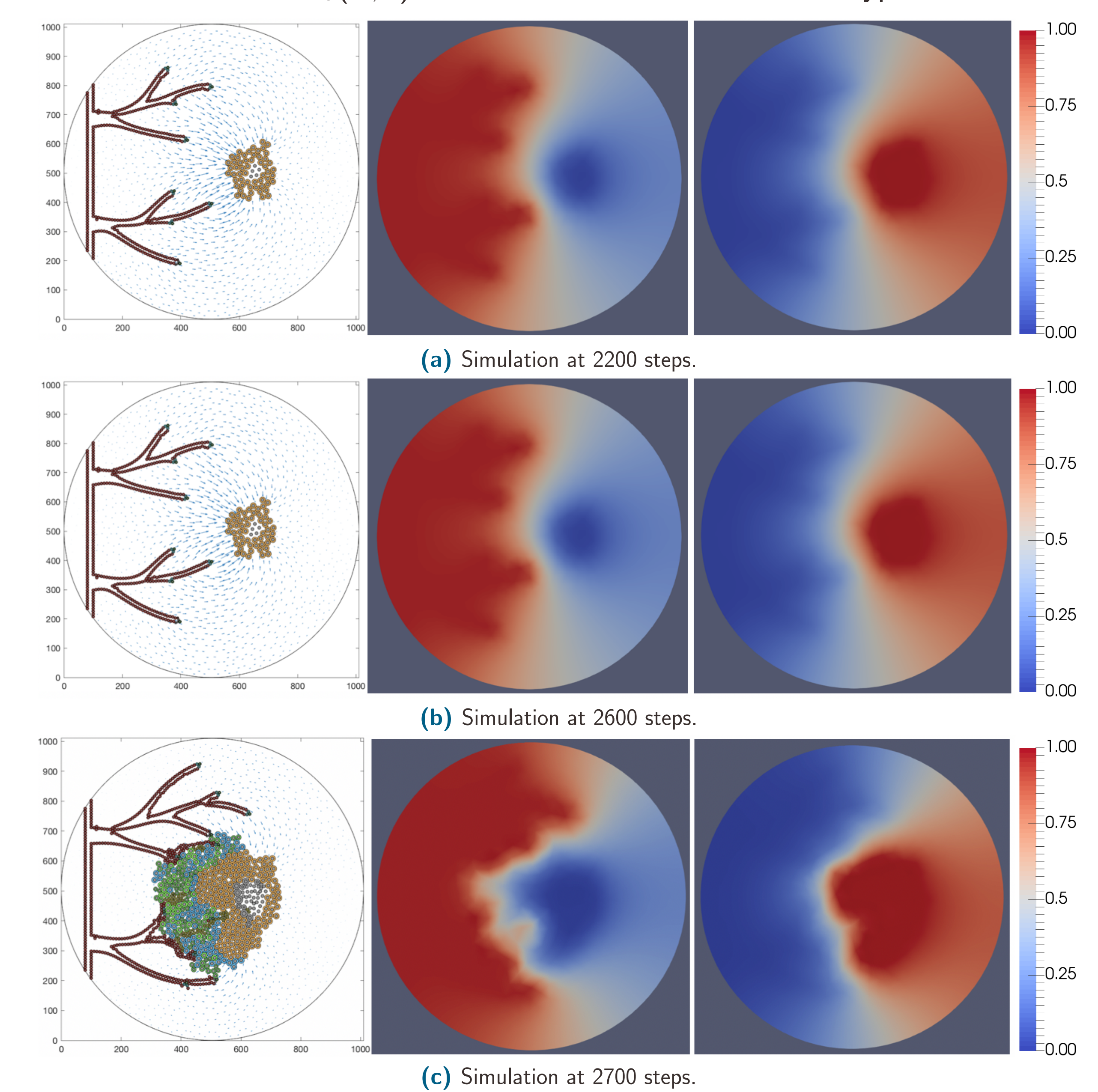


Figure 10: ABM (left), nutrient (middle), and VEGF (right).

Acknowledgments

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